

Magnesium in Drinking Water and Ischemic Heart Disease

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INTRODUCTION

Ischemic heart disease (IHD), codes 410–414 and 429.2 in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) (1), is the leading cause of mortality in many industrialized countries. Among people over age 45 years in the United States, IHD claims more lives per year than any other cause of death. Data from the Third National Health and Nutrition Examination Survey (1988–1991) indicate that an estimated 11.2 million Americans live with IHD (2). In 1992, the most recent year for which mortality data have been published, 480,170 people died of IHD (2). As many as 300,000 sudden cardiac deaths, or even more, occur in the United States each year (3). Because of this heavy population burden of mortality, a factor that prevented even a small proportion of these deaths would save thousands of lives each year and have major public health significance.

In the 1950s, '60s, and '70s, epidemiologists were intrigued when some but not all ecologic studies suggested that "hard" (alkaline) water might have a protective effect against IHD. Many of the waters sampled may have been high in magnesium. Subsequently, in the 1970s, '80s, and '90s, studies have seemed to indicate a beneficial effect of magnesium itself. The preponderance of these population studies of drinking-water magnesium have found odds ratios above 1.0, despite the fact that they must have been carried out with considerable nondifferential exposure misclassification and that the dosage of magnesium derived from drinking water was very small in comparison with usual dietary intake. Besides studies linking magnesium with the development of IHD in the general population—the first stage of pathogenesis—the epidemiologic evidence relates magnesium to three additional points in the natural history of IHD: 1) the point

after the presence of cardiac risk factors has been established; 2) the immediate aftermath of a myocardial infarction; and 3) the years following a first myocardial infarction. This paper reviews the strengths and weaknesses of the epidemiologic evidence relating magnesium to the three stages of the natural history of IHD. We also review the substantial biologic evidence suggesting that magnesium could affect smooth muscle and cardiac muscle irritability, impulse transmission, atherosclerosis, and other physiologic processes which are disrupted in persons with IHD. Finally, a number of possible research options are presented.

MAGNESIUM BALANCE

The human body contains approximately 20,000 mg of magnesium, of which 60 percent (12,000 mg) is found in bone and 20 percent (4,000 mg) in skeletal muscle; the rest circulates in the serum (200 mg) or is divided among other tissues (3,800 mg) (4). The serum level is maintained between 17 mg/liter and 26.7 mg/liter. Approximately 50–65 percent of serum magnesium is in the ionized form (4). With a dietary intake of about 300 mg/day, 200 mg would pass through the body in the feces, and 100 mg would be absorbed into the serum and then excreted in the urine. These estimates do not account for increased loss caused by physical stress and sweating (5). Thus, a typical daily absorption of 100 mg of magnesium is equivalent to 1/38th of the amount stored in tissues other than bone and skeletal muscle. Although it is true that if dietary intake falls dramatically, the kidney is capable of reabsorbing the vast majority of magnesium from the glomerular filtrate, producing urine with almost no magnesium content, a few months of marginally deficient intake could considerably deplete some body compartments of their magnesium (4).

MAGNESIUM TOXICITY

In the absence of renal failure, the kidney is capable of excreting large amounts of absorbed or injected magnesium ion so rapidly that serum levels usually do not become dangerously high (6). The high doses used clinically rarely cause a degree of hypermagnesemia

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Abbreviations: ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; IHD, ischemic heart disease; ISIS-4, Fourth International Study of Infarct Survival; RDA, Recommended Dietary Allowance.

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likely to be associated with serious side effects, because the patients are closely monitored. Potentially toxic and even lethal effects can occur when magnesium-containing drugs, usually antacids or cathartics, are ingested chronically by individuals with renal insufficiency (7, 8). The toxic effects of elevated serum magnesium progress in severity with increasing concentration and include nausea, vomiting, hypotension, bradycardia, urinary retention, electrocardiographic changes, hyporeflexia, central nervous system depression, and, at higher concentrations, life-threatening respiratory depression, coma, and asystolic cardiac arrest (9). A daily intake of several hundred additional milligrams of magnesium from water or supplements can cause diarrhea and abdominal cramps in susceptible individuals (6). After high doses of mostly parenteral application of magnesium, a sharp drop in blood pressure, hyporeflexia, and respiratory paralysis due to central nervous system depression may occur (10, 11). At the most severe level of hypermagnesemia, respiratory depression, coma, and asystolic cardiac arrest may result (9). Clinical experience and the literature show that magnesium has a large therapeutic range. The various randomized trials of post-myocardial infarction magnesium cited below used thousands of milligrams of magnesium per day with no untoward effect. Magnesium hydroxide (milk of magnesia) is an over-the-counter laxative whose prescribed oral dose is 700–1,600 mg/day; thus, a laxative effect is achieved only at doses two orders of magnitude higher than the doses of waterborne magnesium dealt with in the studies reviewed here.

WATERBORNE VERSUS FOODBORNE MAGNESIUM

In the general population, the major portion of magnesium intake is via food and, to a lesser extent, water (12). Balance studies reviewed by Seelig led her to the conclusion that an intake of at least 6 mg/kg per day is needed to ensure adequate magnesium status (13). The Recommended Dietary Allowance (RDA) of 4.5 mg/kg per day is based on the upper range of requirements determined in recent metabolic balance studies (14). Surveys of the food intakes of individuals have revealed that a majority of the US population consumes less than the RDA of both calcium and magnesium; many subjects took less than 80 percent of the RDA for magnesium (8, 15, 16).

Waterborne magnesium has been suggested as a supplemental source of highly bioavailable magnesium (17–20). Two experimental pilot studies (17, 21) using urinary analyses revealed that waterborne magnesium is absorbed about 30 percent better and faster than dietary magnesium. Animal supplementation

studies showed that tap water was more effective in meeting magnesium requirements than dietary supplementation (22). It is possible, then, that waterborne magnesium could correct an insufficient dietary magnesium level (23). Most of the studies discussed below dealt with waterborne magnesium at a level of about 10 percent of total daily magnesium intake. We will discuss below the issue of whether the apparent effects of waterborne magnesium are compatible with the above dietary facts.

DOCUMENTED BIOLOGIC EFFECTS OF MAGNESIUM

Magnesium is a cofactor in more than 300 enzyme systems in human cells, and it has a pivotal position in normal myocardial physiology. Possible sites of action include vascular smooth muscle (24–29), platelets (30–32), and myocardial cells. Animal experimental studies (33, 34) and biochemical laboratory studies (35) show that magnesium is an essential cofactor for sodium-potassium adenosine triphosphatase, an enzyme that influences cardiac irritability by regulating the concentration gradient of sodium and potassium across myocardial cell membranes. The influence of magnesium on the electron transport system is essential for transmembrane ion flux, excitation-contraction coupling, energy metabolism, and prevention of early atherosclerotic changes (36). Magnesium deficiency may be involved in the initiation and propagation of free radical myocardial tissue damage through oxidation of myoglobin, which is essential for intracellular transport and storage of oxygen (37–39). Magnesium helps to suppress arrhythmias during ischemia and reperfusion (40–42). Animals fed on a magnesium-deficient diet developed larger infarcts than did control animals (43). At pharmacologic doses, magnesium is thought to mimic and to be an antagonist of calcium, i.e., a natural calcium channel blocker, possibly because of its structural similarity as a divalent cation (44). Magnesium deficiency in rats causes hyperlipidemia and subsequently atherogenic depositions in coronary arteries, and is involved in the development of endothelial lesions preceding atherosclerosis (45). Arsenian (46) provides a comprehensive review of the available evidence.

CLINICAL TRIALS OF MAGNESIUM AFTER MYOCARDIAL INFARCTION

Very high doses of up to 2,200 mg of intravenous magnesium have been proposed to improve survival immediately after myocardial infarction. It is not clear how relevant any findings from such high doses would be to the prevention of IHD by lower doses. Not all 16 ran-

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domized trials that included magnesium as a treatment option showed a statistically significant benefit. Meta-analyses (47–49) were performed on data from 10 randomized clinical trials in which the clinical use of magnesium in the treatment of arrhythmias, myocardial infarctions, transient ischemic attacks, and hypertension was investigated among 3,900 patients with suspected acute myocardial infarction. Individuals treated with intravenous magnesium postinfarction were at significantly lower risk of dying from IHD-related complications. A review (50) of another five small randomized, controlled trials found that two of them showed a statistically significant reduction in total mortality, and the other three found a nonsignificant trend in the same direction. The Fourth International Study of Infarct Survival (ISIS-4) (51), a large randomized, controlled multicenter trial which showed no beneficial effect on infarct survival or IHD-related complications, failed to produce conclusive results. The use of fibrinolytic therapy post-myocardial infarction before randomization appears to be the most criticized design feature of ISIS-4 (52–54).

There has been one randomized trial (55) of 365 mg of magnesium given orally on an ongoing basis to ambulatory patients who had already had a first myocardial infarction. Surprisingly, the magnesium group showed a statistically significant increase in subsequent myocardial infarctions. If confirmed, this would raise questions about supplementing the water supply of an entire population, which would include post-myocardial infarction patients.

MAGNESIUM AFTER THE PRESENCE OF CARDIAC RISK FACTORS HAS BEEN ESTABLISHED

Singh (56) carried out a prospective 10-year dietary intervention study in India in which 400 urbanized

individuals with prevalent coronary risk factors volunteered to follow either a magnesium-rich diet or their usual diet. A daily magnesium intake of up to 1,400 mg was reached in the intervention group by diet modification without supplements. Intake of waterborne magnesium was not taken into account. There were significantly fewer IHD-related complications in the intervention group ($p < 0.001$), as well as a lower incidence of sudden cardiac death, IHD mortality, and total mortality ($p < 0.01$). Lower fat and cholesterol intake may, among other factors, have confounded the association between magnesium intake and IHD morbidity. It seems likely that Singh observed the effect of various nutritional variables, as affected by the 10-year intervention.

AUTOPSY STUDIES OF MYOCARDIAL MAGNESIUM CONCENTRATIONS

Sharrett (57) and Eisenberg (58) have provided detailed discussions of relevant autopsy studies. Table 1 shows results from studies that specifically dealt with myocardial magnesium concentrations. In none of the studies found in the literature (59–65) did investigators succeed in controlling for the fact that postmortem low myocardial magnesium concentrations may have been a consequence rather than a cause of cardiac death. The studies found that 1) decedents who died from IHD had significantly lower magnesium levels in heart muscle and diaphragm muscle than did decedents who died from accidents and 2) substantially more controls from soft water areas had low magnesium concentrations in coronary arteries than controls from hard water areas. In none of these studies were the statistics adjusted for age at death or stage of IHD. Choosing persons who died via accidents as the con-

TABLE 1. Results from autopsy studies of myocardial magnesium concentrations

Authors and year (ref.)	Location of study	Mean myocardial magnesium content ($\mu\text{g/g}$)*				p value
		Controls†	No. of patients	Sudden deaths	No. of patients	
Chipperfield and Chipperfield, 1973 (59)	England	205	14	172	19	<0.001
Anderson et al., 1975 (60)‡	Canada					
Soft water		918	54	697	27	<0.01
Hard water		982	29	744	12	
Chipperfield et al., 1976 (61)	England	219	12	174	12	<0.001
Chipperfield and Chipperfield, 1978 (62)	England	186	158	154	59	<0.001
Johnson et al., 1979 (63)	United States	221	7	194	14	<0.05
Chipperfield and Chipperfield, 1979 (64)§	England	186	158	179	7	NS¶
Elwood et al., 1980 (65)	England/Wales	181	305	159	489	<0.05

* Wet weight of myocardial tissue.

† Persons who died of trauma, accident, or suicide.

‡ Magnesium content reported for dry weight of myocardial tissue.

§ Sudden infant deaths vs. adult controls.

¶ NS, not significant.

tol group may have introduced confounding bias, because such deaths are often alcohol-related. In addition, chronic alcohol consumption is known to be related to magnesium deficits, but this would have biased differences toward zero (66).

STUDIES OF WATER HARDNESS AND THE POPULATION INCIDENCE OF CARDIOVASCULAR DISEASE

In 1957, Kobayashi (67) first suggested an inverse relation between vascular disease and the acidity of drinking water in Japan; stroke-related death rates appeared to be higher in soft water (higher acidity) areas than in hard water areas. Studies conducted before the 1980s were primarily focused on levels of water hardness. The relevance of these studies to the magnesium hypothesis must be viewed with caution. Extensive reviews by Punsar (68), Neri et al. (69), Comstock (70), and Sharrett (57) failed to find conclusive relations between calcium and magnesium in water and heart disease. Table 2 and figure 1 provide an overview of correlational studies which relate the calcium and magnesium content of drinking water to cardiovascular disease mortality (69, 71-88).

ECOLOGIC STUDIES OF MAGNESIUM IN DRINKING WATER AND IHD

Correlation-based ecologic studies

We found 12 ecologic studies which reported correlation coefficients between rates of IHD (or IHD death) and the magnesium content of local waters (72, 76, 78-80, 84, 85, 87, 89-92). These studies showed contradictory results. Correlation-based ecologic studies may not be optimally sensitive and may not be specific enough to differentiate between a spurious relation and a true relation of water minerals with IHD morbidity and mortality (93). Cardiovascular deaths represent a complex interaction in which lifestyle factors play a large role. Some studies carried out in the United States (84, 85, 94) and in England and Wales (79) showed an inverse correlation between death rates from hypertensive and arteriosclerotic heart disease and calcium and magnesium levels in drinking water. Other investigations in the United States (78) and Canada (90) showed inverse but statistically nonsignificant correlations between magnesium concentrations in water and IHD mortality.

Two Swedish (72, 80) studies demonstrated a relation between water hardness and mortality from arteriosclerotic heart disease, but no relation to magnesium. Both studies had important shortfalls: The average values rather than the mineral levels of individual waterworks were analyzed; magnesium concen-

TABLE 2. Correlation coefficients for water hardness and cardiovascular mortality in various studies

Author(s) and year (ref.)	<i>r</i> ^a	
	Calcium	Magnesium
Eiersteker, 1967 (71)	-0.15	
	-0.46	
Björck et al., 1965 (72)	-0.03	-0.03
	-0.40	0.15
Blachly, 1969 (73)	-0.40	
Crawford and Crawford, 1967 (74)	-0.56	
Dudley et al., 1969 (75)	-0.39	
Elwood et al., 1974 (76)	-0.56	-0.35
Hart, 1970 (77)	-0.46	
Lindemann and Assenzo, 1964 (78)	0.18	0.16
	0.05	0.03
Morris et al., 1961 (79)	-0.54	-0.04
	-0.48	0.08
	-0.54	-0.09
	-0.43	0.05
Nerbrand et al., 1992 (80)	-†	-‡
Neri et al., 1974 (69)	-0.08	-0.10
Roberts and Lloyd, 1972 (81)	-0.46	
	-0.43	
Sauer et al., 1971 (82)	-0.32	
Scassellati-Sforzolini and Pascasio, 1971 (83)	-0.11	
Schroeder, 1966 (84)	-0.51	
Schroeder and Kraemer, 1974 (85)	-0.32	-0.30
	-0.35	-0.28
Shaper et al., 1980 (86)	-§	-‡
Voors, 1971 (87)	-0.35	-0.32
Winton and McCabe, 1970 (88)	-0.32	
	-0.55	

* Pearson's product-moment correlation coefficient. Coefficients listed pertain to different study methods, age/sex groups, and ICD-9-CM codes.

† Significant at the 0.05 level.

‡ Not significant.

§ Standardized regression effect: -3.9%/100 mg of calcium carbonate.

trations were measured years after the disease study period; and areas in which the water composition had changed were not excluded. A cross-sectional study conducted in South Wales which dealt with tap water obtained at home rather than water at the nearest treatment plant (76) failed to demonstrate a significantly inverse correlation between calcium and magnesium and mortality from coronary heart disease and stroke. Shaper et al. (86) found a significant relation between cardiovascular mortality and water hardness in Great Britain, but no association with magnesium. Adjustment for climatic and socioeconomic factors reduced the magnitude of the water hardness effect. The study apparently did not distinguish between IHD and stroke. IHD morbidity in US cities (87) did not correlate significantly with magnesium and calcium in water when the other element was controlled for by partial correlation. Karppanen et al. (95, 96) first implicated the high calcium : magnesium ratio in Finland

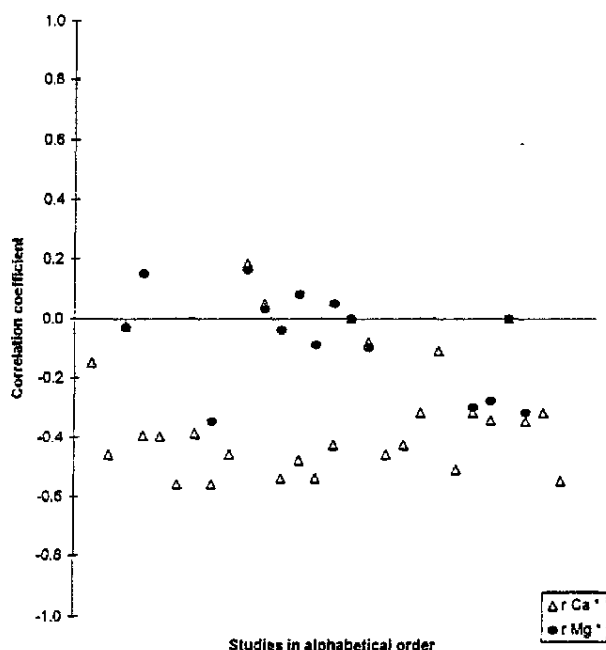


FIGURE 1. Correlations between water hardness and cardiovascular mortality in various studies. Δ , calcium (Ca); \bullet , magnesium (Mg). *r, Pearson's product-moment correlation coefficient. Coefficients shown pertain to different study methods, age/sex groups, and ICD-9-CM codes (see table 2).

in that country's highest IHD and stroke morbidity and mortality among middle-aged men. Later, Marier and Neri (97) demonstrated a significant correlation between incidence of IHD and the dietary calcium: magnesium ratio in various countries.

Rate-based ecologic studies of magnesium and IHD. Rate-based ecologic studies report actual rates, not just correlation coefficients. Table 3 summarizes the characteristics and results of the rate-based studies discussed below. We found eight studies which presented rates of IHD morbidity or mortality as a function of the magnesium content of water. Many of these protective effects resulted from surprisingly low levels of waterborne magnesium. For most of the studies, information on confidence limits, significance tests, detailed assessment of water or nutritional intake, or control for other known risk factors was not presented. The measurement of exposure in all of these studies left much to be desired. The amount of tap water consumed in beverages and in cooking was not ascertained; in addition, information on the magnesium content of the drinking water was obtained from official sources at a convenient time point and sometimes was averaged for areas whose water came from several different water companies. This would have induced considerable nondifferential misclassification as to magnesium intake. Figure 2 shows differences in rel-

ative risks and changes in water magnesium levels in five rate-based ecologic studies which presented their data in a form that lent them to graphic presentation.

An early Finnish study on the relation between fluoride and magnesium concentrations in drinking water focused on the prevalence of cardiovascular disease (98). Water magnesium concentrations showed large variability within the monitored areas. The prevalence of IHD varied markedly and showed no uniform relation with magnesium water levels.

Allwright et al. (99) matched three Los Angeles, California, communities supplied by water of different hardness according to age, sex, race, income, socioeconomic status, and stability of mineral concentrations, using 1970 US Census data. The weighted mean magnesium contents of the drinking water, which had not changed in the previous 10 years, paralleled the concentrations of calcium found in the same areas. When the three areas were compared, there was no change in IHD mortality with alterations in water magnesium and calcium concentrations. Approximately 85 percent of the study population had been exposed to the levels of magnesium found in municipal drinking water. Migration and commuting to other areas of Los Angeles could have introduced misclassification bias as to intake of waterborne magnesium and calcium. This carefully designed study, carried out in a circumscribed geographic area with major IHD risk factors controlled, did not show a significant reduction of IHD morbidity with change in water magnesium levels.

IHD death rates in South African white males showed a significant negative association ($p < 0.02$) with magnesium levels in drinking water (100, 101). No such association could be demonstrated in blacks. However, one drawback of the study was the fact that, while mortality was assessed in 1978, water analyses for the same areas were performed 4 years later.

Teitge (102) conducted a study over a period of 10 years in a district of East Germany. Myocardial infarction incidence and water hardness were compared for hard water versus soft water areas. Magnesium concentrations ranged from 2 mg/liter to 48 mg/liter; the weighted mean magnesium concentrations in five areas varied from 2.9 mg/liter to 5.8 mg/liter. A 38 percent decline in myocardial infarction incidence, from 332 per 100,000 population to 206 per 100,000, was found with increasing concentrations of calcium and magnesium.

Rylander et al. (103) explored water magnesium concentrations in Sweden and found that changes in the magnesium concentration at low levels produced significant differences in the incidence of cardiovascular mortality. Communities with no change in the

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TABLE 3. Rate-based studies of magnesium in the drinking water and diet and ischemic heart disease

Author(s) and year (ref.)	Location of study	Study population	Outcome	Magnesium	Calcium	Observation period (years)	Parameters	RR*	p value or 95% CI*	Attributable risk†
				Level (mg/liter)	Level (mg/liter of CaCO ₃ *)		Rate (per 100,000)			
Ecologic studies										
Luoma et al., 1973 (98)	Finland	300 men aged 24–70 years	Prevalence of IHD*	5.8	N/A*	"Several"	8,600	7.82	—‡	0.87
				11.0			1,100			
Altwright et al., 1974 (99)	Los Angeles, California	n = 244,524, all ages§	IHD morbidity	5.0	82	2	99	1.03	NS*	0.03
				18.0	327		96			
Leary et al., 1983 (100)	South Africa	White males, age N/A	IHD mortality	1.0	N/A	1	500	5.00	p < 0.02	0.80
				45.0	N/A		100			
Telge, 1990 (102)	East Germany	n = 105,000; males and females aged >40 years	Incidence of MI*	2.9	N/A	10	332	1.61	p < 0.05	0.38
				5.8	N/A		206			
Rylander et al., 1991 (103)	Sweden	n = 809,655; males and females, all ages	IHD mortality	1.0	N/A	10	N/A	1.41‡	p < 0.02	0.29
				15.0	N/A		N/A			
Case-control studies										
Luoma et al., 1983 (104)	Finland	Men aged 30–64 years	First MI	<1.2	N/A	2	No. of cases 50	No. of controls 50	4.67‡	1.3–25.32
				>3.0	N/A				1.63‡	0.62–4.52
Rubenowitz et al., 1996 (12)	Sweden	Men aged 50–69 years (median age, 64 years)	Mortality from acute MI	<3.5		8	654	989	1.51‡	p < 0.05
				>9.8					1.00‡	0.34
Cohort studies										
Punsar and Karvonen, 1979 (106)	Finland	Men aged 40–59 years					No. of cases	Sample size		
		Eastern Finland	IHD mortality	3.1 (0.3)‡	Lower	15	121	823	1.57	p < 0.001
		Western Finland		13.1 (2.0)	Higher		77	888		
		Eastern Finland	Sudden cardiac death	3.1 (0.3)			45	823	1.50	NS
		Western Finland		13.1 (2.0)			30	888		0.33
Dietary intervention studies										
Singh, 1990 (58)	India	400 men aged 25–63 years		Intake (mg/day)	Intake (mg/day)					
		Intervention group	IHD complications	1,142 (233)	880 (212)	10	59	206	2.11	p < 0.001
		Control group		418 (105)	512 (150)		117	194		0.53
		Intervention group	Sudden cardiac death	1,142 (233)	880 (212)		19	206	1.58	p < 0.02
		Control group		418 (105)	512 (150)		30	194		0.37

* RR, relative risk; CI, confidence interval; CaCO₃, calcium carbonate; IHD, ischemic heart disease; N/A, not available; NS, not significant; MI, myocardial infarction.

† Attributable risk = (incidence in exposed – incidence in unexposed)/incidence in exposed = (relative risk – 1)/relative risk.

‡ The trend of ischemic heart disease prevalence with increasing levels of waterborne magnesium was not uniform.

§ Communities matched according to age, sex, race, income, socioeconomic status, and stability of mineral concentrations.

¶ Risk estimate provided in original published article.

Numbers in parentheses, standard deviation.

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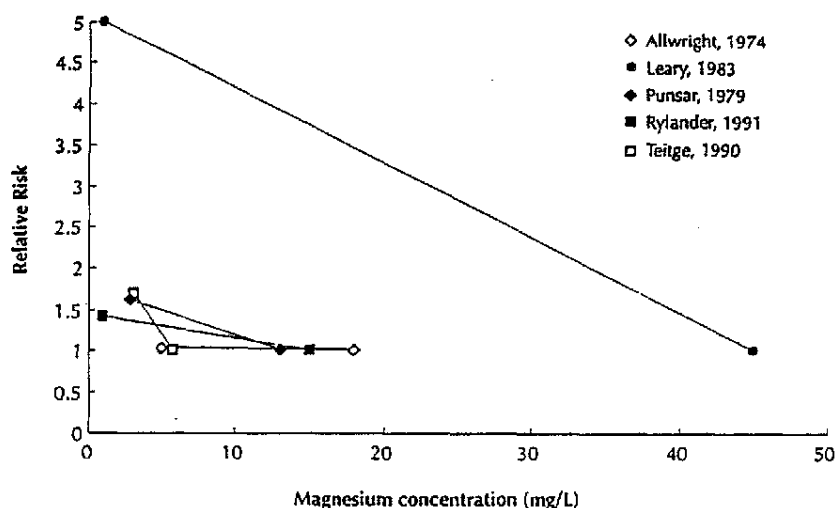


FIGURE 2. Relative risk of ischemic heart disease as a function of water magnesium concentration in five rate-based studies (99, 100, 102, 103, 106).

chemical composition of their drinking water were included in the study. Ten-year death rates for IHD and cerebrovascular disease in 27 municipalities were standardized for age group and related to mortality data for the entire country. Comparison with the expected numbers of deaths showed a decrease in the relative risk from 1.1 for 1 mg/liter to 0.78 for 15 mg/liter.

A recent study conducted in Switzerland (Rylander et al., University of Gothenburg (Gothenburg, Sweden), unpublished manuscript) confirmed the inverse correlation between magnesium in drinking water and mortality from IHD.

Case-control studies. Luoma et al. (104) conducted a retrospective hospital- and population-based case-control study among Finnish males aged 30–64 years, to investigate the effects of magnesium and fluoride on IHD. Fifty myocardial infarction patients were pair-matched for age and region (rural vs. urban). For the population-based case-control pairs, the study showed significantly elevated risk estimates for low magnesium and fluoride concentrations. Exclusion of persons under 50 years of age or persons who had used their present water source for less than 6 years led to increased risk estimates.

A recent retrospective case-control study of Swedish males aged 50–69 years by Rubenowitz et al. (12) addressed the relation between deaths from acute myocardial infarction (ICD-9-CM code 410) between 1982 and 1989 and the level of magnesium in drinking water. Potentially confounding factors such as sex, age, and calcium in drinking water were controlled for, but not risk factors such as diet, exercise, and cholesterol level. Individuals exposed to higher water mag-

nesium levels, ranging from <3.5 mg/liter to >9.8 mg/liter, were at significantly lower risk of death from myocardial infarction. Confounding bias may have been introduced by selecting males who died of cancer (ICD-9-CM codes 140–239) as controls, since there are reports in the literature on an association between magnesium and malignant neoplasms (105). Although this study offered an increase in precision regarding exposure to magnesium, the exact magnesium intakes from water consumed at home or in other places are unknown, because the amounts of water consumed and the use of water filters were not documented. There is also uncertainty regarding the accuracy of diagnosis, which was based on information obtained from death certificates.

Cohort studies. Punsar and Karvonen (106) conducted a prospective cohort study in two rural populations of males in Finland over a 15-year period. Regarding assessment of exposure to magnesium in drinking water, the study had the characteristics of an ecologic analysis. In both study areas, drinking water, collected primarily from wells, was soft. The cohort in eastern Finland experienced a 1.7 times higher death rate from IHD than the cohort in the western part of the country. The two populations seemed to be suitable for a water study, since the men in the two areas led similar rural lifestyles and magnesium levels in drinking water were stable. These data support the hypothesis that magnesium levels in drinking water play a role in the difference between the IHD mortality rates in the two study areas.

Four of five ecologic studies (98–100, 102, 103), one cohort study (106), and two case-control studies (12, 104) showed a beneficial effect of magnesium.

The relative risks clustered around 1.6, ranging from 1.4 to 7.8. The attributable risks ((relative risk - 1)/relative risk) in these studies ranged from 33 percent to 87 percent. The population attributable risk percentage is not available for these studies, because their authors did not provide data on the full distribution of exposures in cases and noncases. Indeed, we have not found published data on the distribution of a population according to their source of waterborne magnesium. As a general observation, it should be noted that few water sources seem to be rich in magnesium, so calculated population attributable risk percentages would not be dramatically smaller than attributable risk percentages.

Dose-response estimates

Assuming a drinking water consumption of 2 liters per day, estimates of changes in the absolute rates and the relative risks of cardiovascular morbidity and mortality were obtained (table 4). The decrease in the absolute mortality rates ranged from 0.1 per mg per 100,000 population in the Los Angeles study (99) to 20.0/mg/100,000 in the Finnish study (106). The relative risk decrease ranged from 0.001 to 0.034 per mg of magnesium. The East German study (102) showed a decrease in the incidence of myocardial infarction of 21.7/mg/100,000: the relative risk decreased 0.105 per mg. The Indian food intervention study (56) showed a decrease in the absolute rates of cardiovascular morbidity of 1.0/mg/100,000, and a decrease in the relative risk of 0.002 per mg. As mentioned above, the control group in this study had a magnesium intake of 300–500 mg/day; for the intervention group, approximately 700–850 mg were added to this diet, which is already rich in magnesium by Western standards. It seems possible that an effect could have been observed

at smaller intervention levels. In reviewing the data in table 4, we assessed whether the absolute or relative effect of magnesium on IHD was an orderly function of the range between high and low magnesium water concentrations. For example, does one reach a point of diminishing returns or, to the contrary, does the effect become larger as the difference between high and low doses of waterborne magnesium becomes larger? We saw no orderly pattern.

RANGE OF APPARENT EFFECTS

How can we explain the seemingly paradoxical finding that waterborne magnesium, which contributes orders of magnitude less magnesium to intake than does dietary magnesium, has such a large apparent effect on cardiovascular health? Calculation of the proportion of total mortality attributable to magnesium deficiency would require knowledge of the current range of intakes. Lacking this information, one could take a hypothetical city with low levels and, on the basis of results derived from the above-mentioned studies, calculate the effect of increasing waterborne magnesium on IHD rates. The calculations suggest that a small percentage change in total dietary intake, through a change in drinking water, might produce dramatic changes in IHD rates. The East German study of IHD incidence by Teitge (102) provides a number of data points from an ecologic study. It also provides one of the steepest regression slope estimates. If we apply this coefficient to a hypothetical city with magnesium levels at 2.9 mg/liter and increase the magnesium levels to 5.8 mg/liter, the IHD rates would fall from 332/100,000 to 206/100,000—an absolute drop of 126/100,000, or a 1.6-fold relative drop. When we express this as a percentage of the higher rate, it represents approximately a 38

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TABLE 4. Range of absolute rates and relative risk gradients for the relation of magnesium intake with cardiovascular morbidity and mortality in various studies

Author(s) and year (ref.)	Outcome	Daily magnesium intake (mg)*			Estimated rate per 100,000 population		Absolute risk gradient† (mg × 100,000 ⁻¹)	Rate ratio	RR‡ gradient§ (1/mg)
		Lowest	Highest	Range	Low intake	High intake			
Allwright et al., 1974 (99)	IHD‡ mortality	10	36	26	99.0	96.0	0.1	1.03	0.001
Leary et al., 1983 (100)	IHD mortality	2	90	88	500.0	100.0	4.5	5.00	0.045
Punsar and Karvonen, 1979 (106)	IHD mortality	6.2	26.2	20	980.0	580.0	20.0	1.69	0.034
Rylander et al., 1991 (103)	MI‡ incidence	2	30	28	(RR = 1.1)	(RR = 0.78)	N/A‡	1.41	0.015
Singh, 1990 (56)¶	IHD morbidity	418	1,142	724	1,800.0	1,070.0	1.0	2.11	0.002
Teitge, 1990 (102)	MI incidence	5.8	11.8	5.8	332.0	206.0	21.7	1.61	0.105

* Consumption of 2 liters of water per day was assumed in order to obtain an estimate of the range of differences in magnesium intake from drinking water or dietary intervention.

† Absolute slope = (rate for low magnesium intake - rate for high magnesium intake)/range (in mg), which has units of [mg × 100,000]⁻¹.

‡ RR, relative risk; IHD, ischemic heart disease; MI, myocardial infarction; N/A, not available.

§ Relative risk slope = (RR - 1)/range (in mg), which has units of 1/mg.

¶ Dietary intervention study.

percent reduction (attributable risk percentage). If, instead, we used the data from Allwright et al. (99), an absolute and relative decrement of only a few percent would be achieved. However, even a few percentage points of difference for a common and serious disease, if real, could be of public health interest. For example, a few percent (not to speak of a hypothetical 38 percent) of the 300,000 fatal cardiac arrests which occur each year in the United States represents thousands of cases per year.

Since migration may have affected the results of the study by Allwright et al. (99), we use Teitge's data (102) to illustrate our point. If one applies Teitge's IHD incidence difference of 126 per 100,000 per year to a city with one million adult inhabitants, the total burden of avoided IHD each year is 1,260 cases. How reasonable is this? Even assuming that typical persons drank 2 liters per day of this water with 5.8 mg of magnesium per liter, they would only be taking in 5.8 mg/day more than they were when the water contained only 2.9 mg/liter. Water intakes less than 2 liters/day would contribute even less waterborne magnesium intake. Investigators such as Marier and Neri (97) argue that such small amounts of waterborne magnesium are effective because other dietary sources of magnesium are grossly deficient. Their arguments are not quantitative, but they seem to us to be saying that these other sources are so low in magnesium that even a 5.8 mg/day difference represents a large percentage supplementation.

Let us assume that the incremental waterborne magnesium needs to represent the same proportion as the corresponding proportionate fall of IHD—38 percent in our example. We do not know what the total dietary East German magnesium intake was at the time of this study, but we can calculate how low the foodborne intake would have to be so that increasing the waterborne intake by 5.8 mg would constitute a 38 percent increase in total intake. Let X be the foodborne intake. When $[(X + 11.6) - (X + 5.8)] / (X + 5.8) = 0.38$, then $X = 9.5$ mg/day. That is, the baseline foodborne intake would have to be as low as 9.5 mg/day for this change of 5.8 mg to constitute a 38 percent increase in total foodborne intake.

Of course, what is important is the absorbed magnesium, not the ingested magnesium. Let us stipulate that waterborne magnesium is absorbed 1.3 times more avidly than foodborne magnesium (17, 21). Assuming 30 percent absorption of foodborne magnesium and 39 percent absorption of waterborne magnesium (1.3×30 percent = 39 percent), it can be shown that a food intake of 27.6 mg of magnesium per day with an increase from 5.8 mg to 11.6 mg of waterborne magnesium daily would correspond to a 38 percent

increase in total absorbed magnesium. This assumes that there is a linear relation between magnesium intake and IHD risk.

Either of these intakes is very low compared with the 329 mg/day of the typical American male (15) or even the 198 mg/day mentioned by Altura and Altura (107). This degree of deficiency seems hard to believe. Such gross deficiency would, one would think, produce acute symptomatology. Furthermore, similar associations with magnesium have been seen in South African whites, Swiss, and Swedes. These are not populations with gross nutritional deficiencies. It makes more sense to assume that the East Germans had an intake similar to that of Americans. This, as we have seen, is somewhere between 198 and 500 mg/day. The added 5.8 mg in this case would thus represent somewhere between 3 percent and 1 percent of the total dietary intake. If people actually consumed only 1 liter of water per day, the percentage would be half as much. Even if we assume that 100 percent of the waterborne magnesium is absorbed and only 30 percent of the foodborne magnesium is absorbed, a person ingesting 200 mg of foodborne magnesium and 11.6 mg of waterborne magnesium daily would absorb 71 mg of magnesium, only 6 mg more than the total 65 mg of individuals with only 5.6 mg of magnesium intake from water. This constitutes a 9 percent increase in absorption, which is not enough to explain a 38 percent change. We have tried simulating situations in which subgroups of the population are particularly deficient in magnesium or, in addition to their deficiency, have an even more striking avidity for waterborne magnesium. None of these scenarios are compatible with the production of a 38 percent change in IHD rate. There is another reason for wondering how such a low percentage increment in total magnesium absorption could produce observable effects: Other dietary sources of magnesium may easily vary 10 percent from day to day and from person to person. It would seem that this small difference from water would be lost in the noise. In short, if we require that a given proportional drop in IHD mortality demands a proportional increase in total magnesium ingestion or absorption, the qualitative arguments, which allege that dietary deficiencies in magnesium explain why small differences in waterborne magnesium can produce moderate benefits in IHD morbidity and mortality, do not hold up.

Could the paradox be explained by proposing that there is some dermal absorption during bathing? We found no studies on this possibility, but it seems unlikely to us. Could it be due to the bioaccumulation of magnesium in vegetables and animal products in regions with high magnesium waters? In that case, the

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water is merely an indicator of total magnesium intake and cannot be used to estimate dose-response relationships. This hypothesis requires that people consume primarily locally grown produce and animal products. This assumption might be true in parts of Europe, but certainly not in the United States. It could be tested by assessing 24-hour urinary excretion in populations in low and high magnesium water areas to see whether excretion is higher than that expected from water ingestion alone. The epidemiologic findings could only be explained by a dose-response curve in which slight changes in proportional intake produce an unproportionally large effect. This would mean that a large proportion of the population was so deficient with regard to cardiovascular outcomes that the dose-response gradient was very steep. Under this view, any increase would produce some improvement until some unknown optimum was reached. Singh (56) was able to show some apparent benefit by manipulating the total diet so as to increase magnesium intake by 700 mg/day in persons whose baseline diet contained 400 mg/day, thus suggesting that this optimum might be quite high, more than 1,000 mg/day. This raises the possibility that chronic disease epidemiologists could provide a substantially different nutritional recommendation than that which nutritionists would provide on the grounds of short-term balance studies.

Human nutrient requirements are generally estimated from the results of depletion and repletion studies, isotopic turnover studies, and balance experiments (108). The most common method of estimating human magnesium requirements appears to be the metabolic balance procedure (109). Balance studies attempt to determine the dosage of magnesium required before the body begins eliminating any excess (109-111). When that point is reached, an adequate intake is assumed. Experts argue about the analytic methods and populations chosen for such balance studies. The challenge lies in getting from an average requirement of some individuals to a dietary recommendation for a population (108). As of this date, the RDAs (14) have not addressed prevention of chronic disease (112). RDAs are considered safe and adequate levels of a nutrient, as part of a normal diet; they apply to healthy individuals and do not cover nutritional needs arising from metabolic disorders, chronic diseases, or drug therapies (14). A variety of host and environmental factors apparently influence magnesium excretion. Ultimately, however, the argument for recommending increases in magnesium intake has had a physiologic basis. If the apparent discordance between physiologic and epidemiologic recommendations were to be sustained, this would have implications for other nutrients as well. For example, a small subsample of the popu-

lation might require more magnesium than others in order to avoid IHD. The prevalence of this hypothetical group might be low enough that few or none of them would show up among subjects in a typical balance study, yet they might account for the majority of the IHD cases. In our extensive readings, we have not found serious pharmacokinetic discussions that postulate which body compartments, rate of exchange parameters, and dose-response relationships could explain the IHD incidence changes associated with small differences in waterborne magnesium. Physiologists and pharmacologists must confer and examine this issue further.

METHODOLOGICAL CRITICISMS

There is really no good way to disprove the possibility that studies which show an association between magnesium levels in water or food and IHD risk are more likely to be published. Studies showing no effect (or no significant effect) of magnesium have been published as well. We think this is an unlikely explanation for the results seen.

Another approach to dealing with possible publication bias is to estimate the number of unpublished negative studies ("fail-safe *N*") necessary to invalidate the overall beneficial effect of waterborne magnesium seen in the eight studies reviewed (113, 114). Meta-analysis of observational studies has been proposed (Egger and Davey Smith, University of Berne (Berne, Switzerland), unpublished manuscript), and the "fail-safe *N*," as well as "funnel plot" statistics, must be computed separately for each type of epidemiologic study. However, information on the rigor of the methods, as well as on parameters required for this type of analysis, has been provided in only a few studies (99, 102, 103). The population sizes in these three studies ranged from 105,000 to 810,000, and the relative risk estimates for IHD ranged from 1.03 to 1.61, whereas studies with fewer individuals or a less rigorous study design produced much higher risk estimates.

Nondifferential misclassification of information on water and magnesium intake has undoubtedly occurred in these studies, but it is unlikely to have produced false-positive results, particularly in eight separate studies with different study designs. Nondifferential misclassification regarding exposure would tend to obscure results, so that, if present, the magnesium effect would be even stronger than that seen in these studies. Nonetheless, future studies—be they randomized trials for IHD patients, case-control studies, or ecologic studies—could all do a better job of quantifying water and mineral intake.

Bias caused by properties of ecologic studies could distort the exposure-disease association (115).

Multiple-group comparison studies, which describe the association between the average exposure level and the disease rate in various geographic areas, are especially prone to this kind of bias. In addition, certain environmental and sociodemographic variables tend to be more highly correlated with each other on a group level than they are on the individual level, a phenomenon called multicollinearity (115, 116). More homogeneous groups or smaller units of analysis could minimize inferential problems in ecologic studies. Comstock's review (70) of hard water studies indicated that most studies conducted within cities or counties showed no association, or even a reversed association of IHD with water hardness.

Except for a few studies (12, 75, 86), the possibility of confounding by other risk factors has not really been addressed to date. There is no reason to believe that persons in low magnesium areas would, for instance, smoke more, have a higher fat intake, exercise less, have more stress, and comprise more Type A personalities than those in high magnesium areas. Nonetheless, future study designs could take potential confounding into consideration and strengthen the evidence.

In our view, confounding by other waterborne or dietary factors associated with magnesium is the most serious concern with all of the studies to date. A full characterization of all water constituents and their ratios has not been part of the analysis. Significantly IHD-protective effects were described—e.g., for fluoride (104) and silicon (85) in drinking water—and although there seems to be a lack of biologic plausibility that would explain why such a relation is causal, these factors could conceivably confound the association between magnesium and IHD. The Singh study (56) involved changing an entire diet, not just supplementation with magnesium. Future studies should carefully document the range of elements and their chemical forms in the waters being studied. In addition, places with high levels of magnesium in drinking water might have high magnesium levels in locally grown food. Analyses of risk should take all of the constituents into account and should characterize the particular chemical forms of magnesium being studied. It would be unfortunate to recommend magnesium supplementation and then learn that magnesium alone, without consideration of its ratio to other chemicals, was not helpful and perhaps even harmful.

FUTURE DIRECTIONS

Our main focus here is on the possibility that magnesium may play a role in the primary prevention of IHD. This preventive effect may be expressed through an increase in dietary magnesium of hundreds of mil-

ligrams per day or through much smaller amounts of magnesium in water or bottled beverages. It could well turn out that the paradoxical low dose water findings are an anomaly, while the dietary association might be confirmed. Any serious study of waterborne magnesium would need to control for dietary magnesium. The following types of additional studies of the low dose water findings should be seriously considered.

First, we should review ongoing or completed IHD cohort studies to determine whether either the waterborne magnesium hypothesis or the dietary magnesium hypothesis could be evaluated in them. Ideally, such studies would have obtained dietary and medication histories and would have patient addresses available so that local water quality data could be linked to patient records. For example, available data on magnesium laxative use from large IHD cohort studies should be reviewed to see whether individuals exposed to laxatives containing magnesium salts are at lower risk for IHD.

Second, we should conduct a large, nested case-control study of myocardial infarction with and without sudden death in an area with naturally occurring high and low levels of magnesium in the water. Dietary and waterborne intakes could be ascertained in a random validation sample prospectively; then, as cases occurred, cases, surrogate relatives, and controls could be interviewed retrospectively about their diet, vitamin and mineral intake, water intake, and other cardiac risk factors in the recent and more remote past. Waters should be sampled for all minerals and analyzed for their chemical composition. Determining urinary magnesium and food sample magnesium in a subsample of cases and controls in high and low waterborne magnesium areas could address the food bioaccumulation theory mentioned above. Rylander and colleagues are currently conducting a study with some of these features in Sweden; this should also be done in the United States.

Third, the autopsy studies (59–65) suggested that magnesium levels in the myocardium and diaphragm among subjects who died accidental deaths were lower when the drinking water level in the area of residence was low. A confirmation of these findings in a larger, well-conducted study would increase the credibility of the waterborne magnesium findings. A study of the magnesium content of the myocardium, skeletal muscle, bone, and the arterial wall in accident victims of various ages with no detectable alcohol in their blood could be conducted in areas with high and low levels of waterborne magnesium.

Fourth, the ability to benefit from waterborne magnesium supplementation in the face of overall dietary magnesium deficiency could only result from an un-

usually low, genetically controlled ability to absorb magnesium from food coupled with an unusually high absorption of magnesium from water. Such persons might be more prevalent among myocardial infarction survivors than among age-matched persons without IHD. One could carry out metabolic balance studies using foodborne and waterborne magnesium sources to determine whether such people exist and, if so, their prevalence in IHD and normal populations.

It is essential to understand the dose-response relationships between magnesium and IHD, both to increase the credibility of the epidemiologic findings and to guide the recommendations given. Nutritionists and pharmacologists should conduct theoretical studies using quantitative pharmacokinetic models to suggest how it would be possible for one body compartment to become substantially depleted with a slightly deficient diet. Additionally, how would it be possible for waterborne magnesium to have such a marked effect when it constitutes only a few percent of total intake or absorption? Second, animal studies of dose-response relationships in the protection against an atherogenic diet could be carried out. Third, additional studies of the uptake of foodborne and waterborne magnesium from different chemical compounds could be conducted. This would also provide information that could guide medical recommendations regarding supplement use if it were eventually indicated.

STUDIES OF THE UNTOWARD EFFECTS OF MAGNESIUM

Transient gastrointestinal symptoms

Studies should be conducted to determine the rate of untoward gastrointestinal symptoms related to various forms and doses of waterborne magnesium in combination with other minerals, and to discover whether there is a range of inherent sensitivities. Is there habituation to high magnesium levels, or is this side effect permanent? Studies which could address these issues include short cohort studies of populations, such as college students or soldiers, that are moving into areas with high and low levels of magnesium, to determine the incidence and duration of gastrointestinal symptoms. Gastrointestinal side effects could be monitored in large-scale clinical trials or in the control group of any large nested case-control study.

Possible untoward effects of magnesium on other diseases

Morris et al.'s study (79) examined patterns of death rates for a variety of causes of death as they related to water hardness. The overall death rate was lower in hard water areas. A few causes of death had elevated

rates in one sex or the other. The study reported a correlation of community rates with their levels of water hardness. This study should be repeated with better methodology, which could be achieved if the ecologic studies also considered other causes of death. A case-control study could examine a sample of non-cardiovascular deaths to see whether history of magnesium intake was any different from that of controls in these subjects. This type of study could also be used to obtain more complete information on subclinical adverse effects of intermediate to high magnesium intakes—for instance, undesirable changes in blood levels of other nutrients. Any large-scale trials could examine the incidence of other diseases in the treatment groups.

SUMMARY AND CONCLUSIONS

The associations found in the general populations of a number of different countries are suggestive and warrant an integrated program of laboratory and epidemiologic research to reject or confirm the magnesium-IHD hypothesis. Singling out this particular risk factor has two justifications. First, as would be the case with any epidemiologic risk factor for IHD whose attributable risk was large enough to be detectable through epidemiology, applying that attributable risk to the vast annual morbidity and mortality from IHD would translate into tens of thousands of lives benefited and millions of dollars in hospital costs avoided per year. Second, this particular risk factor could conceivably be eliminated by an inexpensive supplementation program. For example, a low-sodium, higher-magnesium and -potassium table salt has been recommended and used in Finland for many years, during a period when the prevalence of hypertension in population surveys was said to decrease (117). Interventions which do not require behavioral change have always been the most cost-effective in public health. We therefore urge funding agencies to give priority to studies determining whether there are unforeseen adverse effects of magnesium for some population subgroups and whether the apparent benefit derived from low doses of magnesium in the development of IHD or IHD death is real. Furthermore, researchers should determine which chemical form of magnesium is best absorbed and most effective.

We need to better understand the interrelation of various water and food constituents, as well as individual risk factors, in the pathogenesis of IHD. Susceptible individuals who are at higher risk of being depleted of magnesium need to be identified, and potential untoward effects of magnesium should be studied. Future research must provide better answers

about low level waterborne magnesium before recommendations to the public can be made.

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